DEVELOPMENT AND EVALUATION OF NON-ENZYMATIC GLUCOSE SENSOR BASED ON METAL PARTICLE/CONDUCTING POLYMER COMPOSITES

SHORT SYNOPSIS

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Certificate

I hereby declare that the short synopsis "**Development and Evaluation of Non-Enzymatic Glucose Sensor Based on Metal Particle/Conducting Polymer Composites**" being submitted in partial fulfillment of the requirement for the degree of Doctor of Philosophy in Department of Chemistry under Faculty of Engineering & Technology of Manav Rachna International Institute of Research & Studies, Faridabad during the academic year 2018-19.
It is a bona fide record of original work carried out under the supervision of Dr. Pradeep K. Varshney & co-supervision of Dr. Yijun Tang and has not been submitted in full or part to any other university or institute for degree or diploma. Further, it is certified that short synopsis is plagiarism free and proof has been submitted.

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ABSTRACT

The integration of polymer films plays vital role in improving the performance of electrochemical devices. These polymer films provide active site for immobilization of metal nanoparticles that have shown to contribute towards the better performance of electrochemical devices. Various conducting polymer-metal nanoparticles composites have been researched which enhances the electrocatalytic behavior of the device. These have found application in improvement of sensing capabilities of glucose sensors. The demand for detection of glucose has led to the advancement in the development of ideal non-enzymatic glucose sensor. The present work is aimed towards the investigation of various conducting polymer-metal nanoparticles composites in fabrication of non-enzymatic glucose sensor. The main objective of the present work is to characterize and fabricate novel polymer—metal composites based glucose sensors. The existing electrode will be modified based on these polymer-metal composites under optimum growth conditions. The characterization and evaluation of various analytical factors such as selectivity, stability, sensitivity, reproducibility, repeatability, and detection limit will be investigated by cyclic voltammetry (CV) and chronoamperometry (CA) techniques. Finally, applicability of the as-prepared non-enzymatic glucose sensor will be studied for glucose detection in variety of juice samples and the obtained results would be compared with commercial glucose meter reading.

Key words: Electrochemical Devices, Glucose Sensor, Non-Enzymatic, Cyclic Voltammetry, Conducting polymer, Composites

CONTENTS

S. No.	Description	Page No.
1	Introduction	1-2
2	Literature Review 2.1 Historical Survey 2.2 Types of Amperometric Glucose Sensors 2.3 Need for Non-Enzymatic Glucose Sensors	2-6
3	Description of Broad Area	7
4	Motivation of the Study	7-8
5	Objectives of the Study	8-9
6	Methodology to be Adopted	9
7	Expected Outcome of the Research	9-10
8	References	10-15

1. **Introduction**

The need for development of ideal electrochemical storage devices is increasing day by day. These find applications in sensors, super capacitors, and fuel cells (Wang et al. 2013; Newman & Turner 2005). In general, all the electrochemical devices compromise of a cathode, an anode, and an electrolyte. The working of these devices is based on the electric current that is developed due to the movement of ions from anode to cathode (Mac Callum & Vincent 1987, 1989). The scientific evaluation of recent years presents us the information that sensors have been fabricated based on composition of electrolyte or modification of the electrode for better performance (Varshney & Gupta 2011; Yang & Hou 2012).

Of the different electrochemical devices, glucose sensors particularly gained our attention. Glucose plays a significant role in almost all physiological processes extending from biomedical to environmental and food (Rocchitta et al. 2016). Therefore, the development of glucose biosensor is immensely growing research area and it has accounted for more than 85% industry of biosensors (Wang 2008). The need for detection of glucose has lead to the development of stable and accurate glucose sensors. The research on glucose sensors has been taken over a decade. Major scientific and technological progresses have been implemented to enforce an ideal amperometric glucose sensor in all fields (Deng et al. 2008). Glucose oxidase (GOx) seems to be an ideal enzyme to fabricate a stable glucose sensor. However, still many challenges have to be overcome for a stable, reproducible, simple, long shelf life, and non-invasive glucose sensor (Pohanka et al. 2008). Of the major challenges, glucose sensors have slow response time and low thermal stability that set back them from use in prominent areas such as health, food, beverages, and fermentation where continuous monitoring of glucose is desired (Cui 2006).

The research in the invention of non-enzymatic glucose sensor aims at developing highly stable, sensitive, reproducible and fast responsive sensors (Çiftçi et al. 2016). Different approaches have been developed till date to find all these parameters in a single glucose sensor. In this context, several modifications have been carried out with electrolyte or the electrode. The use of conducting polymer-metal nanoparticles composites have been shown to rule out the shortfalls of using either nanoparticles or only polymer films (Wu et al. 2013). The blend

of sensor technology and nanotechnology acts as a market propeller in the development of glucose sensors. Noble metal nanoparticles such as Pt (Wang et al. 2014; Ma et al. 2015; Chang et al. 2014), Au (Rao et al. 2017; El-Ads et al. 2015) and Pd (Ye et al. 2015; Singh et al. 2014) have oriented progress towards research in the field of sensors by reducing the response time to 3–10 s and increasing the sensitivities from 1.2 $\mu mM^{-1}cm^{-2}$ – 120 $\mu AmM^{-1}cm^{-2}$ (Hasan et al. 2012). However, still much of the attention is needed towards development of glucose sensors that are thermal stable along with high sensitivity, stability, and wide linear range.

Glucose sensors are classified as enzymatic and non-enzymatic sensors. Research in the area of enzymatic glucose sensors has established the fabrication of highly efficient glucose sensors in terms of sensitivity, stability, selectivity, and cost (Rothwell et al. 2010, Tian et al. 2014). However, the major challenge with enzyme based glucose sensors is that they are not stable as enzymes lose their activity due to variation in temperature, humidity, and pH (Cui et al. 2016). To overcome drawback of enzymatic glucose sensors, research has been focused towards development of non-enzymatic glucose sensors. In latter sensors, the oxidation of glucose occurs directly on the electrode's surface in the presence of metal nanoparticles that acts as catalyst.

2. **Literature Review**

The research in the field of glucose sensors have taken over five decades. Continuous efforts have been put on towards fabrication of ideal glucose sensors. This section describes historical background and three generations of the glucose sensors. Finally, the section concludes with the need for non-enzymatic glucose sensors compared to enzymatic glucose sensors.

2.1 **Historical Survey**

In 18^{th} century, the great scientist Alessandro Volta was named as "Father of Electrochemistry" with the invention of "electric pile" which reformed the period of electrochemical devices. The design was based on the Galvanic cell invented by Luigi Galvani with the research on 'current flow". After the birth of Electrochemistry as Science, researchers focused on

fabrication of these electrochemical cells by using different approaches such as modification of electrode materials, different aqueous salt solutions as electrolytes.

With the advancement in technology, electrochemistry acquires an important part of Chemistry in which different materials and combinations have been used to overcome the need of ideal electrochemical cells. In context of this, the research in the field of conducting polymers-metal nanoparticles composite is in development phase with different rewarding features that includes electronic and ionic properties, electrochromism, semiconductor behavior, and electroluminescence. The electrochemical cells consist of cathode, anode and electrolyte. The combination of different polymers/metal composite being researched provides new opportunities of developing high performance electrochemical devices to be used commercially. Different types of polymers are being utilized in electrochemical devices. The electronically conducting polymers in the composites are being used as modification to working electrodes, ionic conducting polymers are utilized in solid electrolytes, and optically transparent plastic electrodes are for construction of optical or electrochemical devices.

The detection of glucose in almost every field has led to the need for developing ideal glucose sensors. The word sensor origins from the Latin word “sentire” that means ‘to perceive’ (Harries 2006). It is an instrument that acts in response to stimulus by producing a functionally linked output. The measurable properties of the sensor such as capacitance, conductivity, and mass can be altered in presence of different analyte or with change in environmental conditions.

The research in the area of glucose sensors took a leap in 1962 with the advancement of enzyme based sensor by Clark (Clark et al. 1962). Their research was based on measuring oxygen consumption due to glucose oxidation occurring in presence of oxygen. The problem of generation of background oxygen was corrected by Updike (Updike & Hicks 1967) who developed oxygen sensors. From then, the scientists have contributed in developing reliable and stable glucose sensors in the fields of clinical analysis (Malhotra & Chaubey 2003), fermentation (Tothill et al. 1997; Yu et al. 2005), drug (Yu et al. 2005), food (Terry et al. 2005), environmental (Baeumner 2003), and beverage (Monosik et al. 2012). Different techniques have been employed to measure the level of glucose occasionally or continuously.

These include electrochemical, spectroscopic, fluorimetry, and chromatography techniques. The electrochemical methods can be amperometry or potentiometry, whereas spectroscopic, fluorimetry, and chromatography are mainly photonic method (Rahman et al. 2010). Of the different techniques, electrochemical method is preferred for analysis of glucose preferably due to high selectivity and sensitivity, low cost, fast and easy procedure.

The enzyme GOx has been preferred for glucose biosensors due to its stability, low detection limits and higher sensitivity and selectivity (Shrivastava et al. 2016). Much of the research work has been carried out on enzyme based glucose sensors. However, the fabrication of these sensors is a complex process and their reproducibility is of great concern. As the measurements are based on the oxidation processes by the enzymes, the latter are greatly influenced by the changes in environmental conditions and the presence ionic detergents in the sample (Wilson & Turner 1992). These challenges have urged the research on non-enzymatic glucose sensors.

2.2 **Types of Amperometric Glucose Sensors**

The research in the development of glucose sensors has been going on for a decade. Based on the development and research in this field, glucose sensors are classified into major four generations. In the first generation measurements of glucose concentration are based on the production of hydrogen peroxide (H_2O_2). The flavin group (FAD) of GOx is reduced to $FADH_2$ (Eq. 1) which then reacts with free oxygen forming enzyme FAD (Eq. 2) (Koopal & Nolte 1994).

$$GO_x(FAD) + \text{Glucose} \rightarrow GO_x(FADH_2) + \text{Gluconolactone} \quad (1)$$

$$GO_x(FADH_2) + O_2 \rightarrow GO_x(FAD) + H_2O_2 \quad (2)$$

The major drawback of the first generation glucose sensors was that measurement of H_2O_2 requires high potential. Another issue is the oxygen dependency of these sensors which can result in fluctuations in the measurements. Much of the research work has been done to overcome these challenges (Karyakin et al. 1995; Karyakin et al. 2002; Karyakin et al. 2000).

In lieu of further improvement, second-generation enzyme glucose sensors were introduced. In this generation, a mediator was introduced in replacement of the oxygen. GOx is not able to

transfer electrons directly thus mediators were introduced such as ferrocyanide, quinones, and ferrocene derivatives. These mediators bind with the active site of the enzyme, thus facilitating electron transfer from redox centre of the enzyme to the surface of electrode. This resulted in detecting concentration of glucose even at low levels (Mayorga et al. 2011). It is required that the mediator remains to the electrode and near the enzyme which is quite difficult to achieve (Heller & Feldman 2010). Moreover, mediator being the size of oxygen may compete with oxygen during the reaction. Hence, these sensors require more complicated fabrication process.

The third generation sensors overcome the drawbacks of second generation and aim towards mediator free system. In this, the electron transfer takes place directly between the enzyme and electrode (Chu et al. 2015; Jindal et al. 2014). This would result in fabrication of highly selective and unhindered system. Mesoporous electrode surface have been researched for the direct electron transfer between electrode and enzyme (Sugimoto et al. 2016; Christiansen et al. 2013).

It is the need of glucose sensor technology to build a sensor with high stability, sensitivity and reproducibility. Non-enzymatic glucose sensors constitute the fourth-generation glucose sensors. About a decade ago, the investigation of non-enzymatic glucose sensor was carried out by Loeb (Loeb 1909). In non-enzymatic sensors, atoms are present at the surface of electrode that acts as catalysts. Nanomaterials have been used over the electrodes to increase the surface area, conductivity, and mass transport ability. Different nanoparticles act as electrocatalysts and can carry out the oxidation reaction on non-enzymatic glucose sensors. These include transition metals (Pt, Ni, Ag, Cu, Au), metal oxide (CuO, IrO_2), alloys (Pt-Pb, Pt-Ir), nanowires, mesopores and carbon (Carbon nanotubes).

2.3 **Need for Non-Enzymatic Glucose Sensors**

The research on glucose sensors has been taken over a decade. Major scientific and technological progresses have been implemented to enforce an ideal amperometric glucose sensor in all fields. GOx seems to be an ideal enzyme to fabricate a stable glucose sensor. However, still many challenges have to be overcome for a stable, reproducible, simple, long shelf life, and non-invasive glucose sensor.

Challenges with Enzymatic Glucose Sensors

a. **Stability and Sensitivity**: The major drawback with the enzymatic glucose sensor is the stability of enzyme which is lost due to change in temperature, pressure, humidity, or pH. Though, GOx has been proven to be much stable enzyme, still it loses its activity due to environmental changes. Wilson and Turner (Wilson & Turner 1992) and other references (Caras et al. 1985; Li & Lin 2007) have cited in their review that GOx is stable only in the pH limit of 2 to 8 and maximum temperature of 40°C. Beyond these conditions, it loses its activity. Moreover, ionic detergents have shown to cause fatal damages to this enzyme. Thermal instability of GOx hindered its reaction mechanism in the glucose sensor. Even, the low and high conditions of humidity are not suitable for the activity of GOx to be used in sensors. These challenges have urged the research on non-enzymatic glucose sensors.
b. **Simple and Reproducible:** The fabrication of enzyme based glucose sensors requires vigilant ways of immobilization on the electrode surface. Many of the complicated processes have been proposed in this regard, such as electropolymerization (Rothwell et al. 2010), optimized cross-linking on nanotube arrays (Wang et al. 2014), simple adsorption, adsorption and BSA blocking and many more (Nery & Kubota 2016) ensuring reproducibility, stability and lower cost. The reproducibility of these enzymatic glucose sensors remains an issue as the performance of these sensors is dependent on activity of immobilization of enzymes.
c. **Oxygen Dependence**: It has been reported that low limits of oxygen regulates the enzyme. The major drawback of the first generation enzyme was the oxygen dependency. This was overcome by using mediators in the second generation, but this resulted in more complicated process of setting up the system. Hence, it was absolutely required to keep the reactions non-dependent on oxygen or to attain the kinetics at slower rate (Collier & McShane 2015).

Considering these problems, the research on non-enzymatic glucose sensors seems promising, still many enzyme based glucose sensor remain in practical use.

3. **Description of Broad Area**

Over the last four decades, the conducting polymers are used as progressive material for electrochemical devices due to its simple fabrication process, strong interfacial contact with electrodes, stability in terms of mechanical, conducting and electrochemical. Still, there is wide need to improve the mechanical and conducting nature of the polymers that would further improve the performance of electrochemical devices.

Glucose sensor is an immensely growing research area in electrochemical devices worldwide. Various efforts have been made in development of better performing glucose sensors. Research has been focused in developing ideal glucose sensor in terms of stability, selectivity, sensitivity, reproducibility, low detection limits, fast response time, and wide linear range. Researchers have reported the use of metal-polymer composites to attain all these parameters in one electrode (Rocchitta et al. 2016). Various conducting polymer films have been investigated for oxidation of glucose due to their mechanical and conducting properties. These include polyaniline (PANI) (Zhou et al. 2005, Ghanbari & Babaei 2016), polypyrrole (PPY) (Tilagam et al. 2015), polythiophenes (Hocevar et al. 2016), poly(ophenylenediamine) (PoPD) (Liu et al. 2015), poly (3, 4-ethylenedioxythiophene) (PEDOT) (Mazloum-Ardakani et al. 2016), and polyvinylferrocenium (Sahin et al. 2013). The polymer film formed on electrode surface is stable and provides active site for the dispersion of metal particles. The integration of noble metals (Pt, Au and Pd etc) on the conducting polymer film acts as catalyst that increases the oxidation reaction of glucose. The electrocatalytic behavior of the metal nanoparticles is greatly influenced by certain factors such as substrate concentration, method of preparation, deposition time, particle size, and temperature. In general, the catalytic behavior increases with increase in concentration of substrate and small particle size (Wu et al. 2013).

4. **Motivation of the Study**

The need for glucose sensors is increasing day by day. In this perspective, an ideal glucose sensor is desirable that is reliable and accurate. Enzyme based glucose sensor are not stable due to loss in activity of enzymes. Addressing to these challenges, non-enzymatic sensors have attracted interest for detection of glucose. The fabrication of non-enzymatic glucose sensors

requires catalytic action of metal nanoparticles for the oxidation of glucose. The development process of non-enzymatic glucose sensor proposes the use of conducting polymer-metal nanoparticles that adhere to the electrode surface. This motivation will help to research for polymers that are conducting and would provide matrix for immobilization of the electrocatalytic metal nanoparticles. Also, the research would be focused on research of noble metal nanoparticles that would provide large surface area for better performance of the sensor. The modification of the working electrode with suitable metal nanoparticles-conducting polymer composites would be employed towards developing highly stable, reproducible, sensitive, selective, and cost-effective non-enzymatic glucose sensors.

5. **Objectives of the Study**

The need for glucose sensors is increasing day by day. In this perspective, an ideal glucose is desirable that is highly reliable, accurate, stable, sensitive, and selective. This research work would be focused towards developing non—enzymatic glucose sensors based on different metal nanoparticles/conducting polymer composites. Following objectives have been proposed to be achieved by the end of this Ph.D research work:

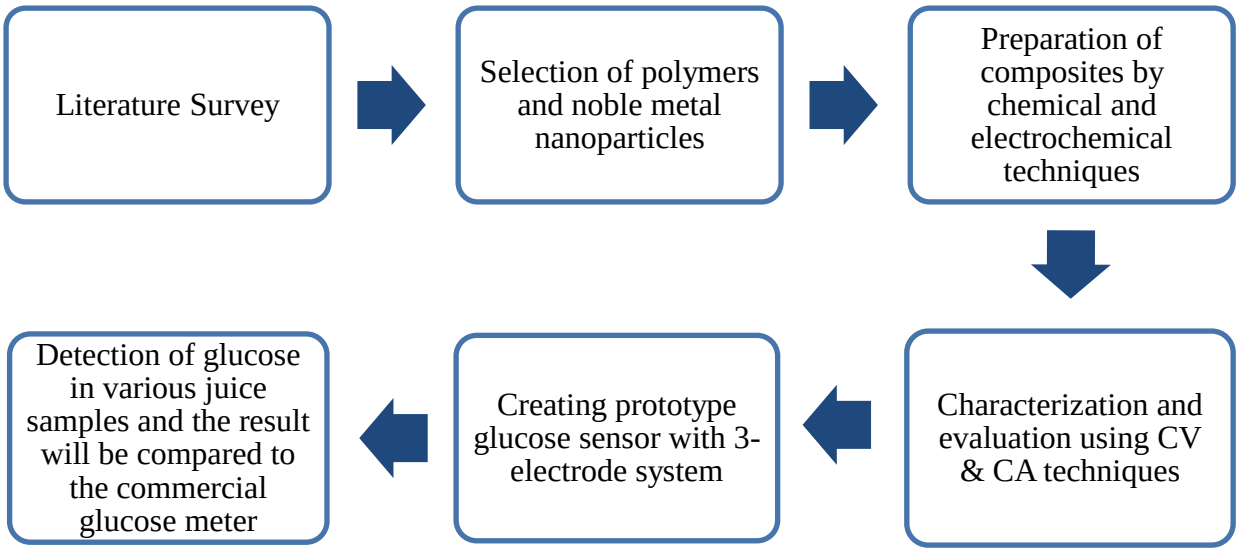
i. To develop non-enzymatic sensor for detection of glucose based on modification of electrode with conducting polymer-metal particles composite.
ii. To develop non-enzymatic sensor of high sensitivity, less response time, wide linear range, and enhanced stability.
iii. To study the optimum growth conditions of metal nanoparticles for maximum dispersion on polymer film for better performance of the glucose sensor.
iv. To study the characterization of the modified working electrode using cyclic voltammetry (CV) technique.
v. To evaluate the various analytical parameters such as sensitivity, selectivity, detection limits, response time using chronoamperometry (CA) technique.
vi. To assess the anti-interference property of the sensor in presence of various interferents (uric acid, ascorbic acid, and sucrose).
vii. To study the reproducibility, repeatability, and stability of the sensor using CV technique.

viii. To fabricate the prototype non-enzymatic glucose sensor based on 3-electrode system where working electrode is modified Pt, counter electrode is Pt wire and reference electrode is SCE.

ix. To study analytical practical applicability of the sensor in glucose detection in various juice samples and comparing results with commercial glucose meter.

6. Methodology to be adopted

The main objective of the proposed work is to fabricate prototype non-enzymatic glucose sensors based on conducting polymer-metal particle composites. The methodology to be adopted for conducting the study has been described in the given flow chart.


Literature Survey
Selection of polymers and noble metal nanoparticles
Preparation of composites by chemical and electrochemical techniques
Characterization and evaluation using CV & CA techniques
Creating prototype glucose sensor with 3-electrode system
Detection of glucose in various juice samples and the result will be compared to the commercial glucose meter

7. Expected Outcomes of the Research

The expected research outcome of the proposed research work would be the availability of a scientific database containing design, characterization and fabrication of a new technique based economical conducting polymer-metal nanoparticles composite films and of technical data regarding their device applications. The contribution of these composites would fulfill the requirements towards development of stable glucose sensors. Thus, the proposed work is

aimed towards exploration of patent-able components of the research outcome at every stage of the investigation followed by dissemination of those publishable results in national and international journals in the field of Sensors. The proposed research outcome will also contribute towards the challenges faced by existing glucose sensors and will have profound influence on the detection of glucose in all fields.

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